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#20

Attorney Docket :
032340 WN 004

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:	)	
Peter Kótay NAGY, et al.	)	
US Serial No.: 09/701,732	)	Group Art Unit: 1624
Filed: December 4, 2000	)	Examiner: Bernhardt, E.

For : PROCESS FOR THE PREPARATION OF A 3/2H/-PYRIDAZINONE-4-SUBSTITUTED AMINO-5-CHLORO-DERIVATIVE

DECLARATION UNDER 37 C.F.R. §1.132

Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Declaration of Dr. József Barkóczy

I, József Barkóczy, declare as follows:

1. I am a Senior Research Scientist at Egis Gyógyszergyár Rt. and live at H-1016, Szirom u. 4-6/B, Budapest, Hungary. I am a person of skill in the technical discipline of the present invention. Attached hereto is a copy of my curriculum vitae.

2. I have read U.S. Patent Application. No. 09/701,732 entitled "PROCESS FOR THE PREPARATION OF A 3/2H/-PYRIDAZINONE-4- SUBSTITUTED AMINO-5-CHLORO- DERIVATIVE" including the currently pending claims in that application,

melt reaction mixture was stirred at this temperature for 5 hours and cooled to room temperature. 20 ml water were then added and the mixture was extracted three times with 20 ml of ethyl acetate each. The united organic layers were dried over magnesium sulfate and evaporated *in vacuo*. This resulted in 3.1 g of an oily residue. As an example of the present invention, a product was obtained using the process of the present invention (see Attach. B).

6. As shown in Attach. A, according to HPLC analysis, the product which resulted from the Zara method contained 84.7% of the desired 5-chloro-4-(3-{[2-(3,4-dimethoxy-phenyl)-ethyl]-methylamino}-propylamino)-2H-pyridazinone-3-one and 3.7% of a dimer contamination corresponding to the formula 5-chloro-2-[3-(5-chloro-3-oxo-2,3-dihydro-pyridazine-4-yl-amino)-propyl]-4-(3-{[2-(3,4-dimethoxy-phenyl)-ethyl]-methylamino}-propylamino)-2H-pyridazine-3-one. In addition, to the above contaminant, further impurities were also formed in a significant amount which are not formed in the process of the present invention. Furthermore, the oily product resulting from the method of Zara cannot be further purified by crystallization. The product resulting from the method of Zara can only be purified by chromatographical methods which are unsuitable for industrial scale production. In contrast, according to the present invention, the product obtained from the method of the present invention contains 99.78% of the desired compound and an insignificant amount (0.05%) of the undesired dimer. Accordingly, the process of the present invention enables the preparation of the desired compound at a purity which complies with the requirements of the Pharmacopoeia, even on an industrial scale.

7. Accordingly, it is my opinion that the Zara process is completely different from the present invention. Moreover, the method described by the Zara document fails to yield a

product that has the superior and unexpected properties of the product yielded by the inventive method with respect to product purity as demonstrated by the attached results of the side-by-side comparison.

8. I declare, under penalty of the perjury laws of the United States, that all statements made herein of my own knowledge are true and that all statements made based on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

Respectfully submitted,

By : _____
József Barkóczy

Date Signed : March 19, 2003.

Curriculum Vitae

Pers nal data:

Name: Dr. Barkóczy József
Date of birth: May 6, 1954
Place of birth: Budapest, Hungary
Citizenship: Hungarian
Profession: pharmaceutical research engineer
Home address: 1016 Budapest, Szirom u. 4-6/b., Hungary
telephone: (36-1) 386-4745

Tertiary education:

Dipl. Ing., M.Sc.
Technical University of Budapest
School of Chemical Engineering
Faculty of Organic and Biological Chemical Engineering
Duration: 1972-1977
Date of issue: June 9, 1977
Place of issue: Budapest, Hungary
Number of diploma: 84/1977

Additional education:

Achievement of postgraduate degree in pharmaceutical chemistry as specialized pharmaceutical research engineer
Technical University of Budapest
School of Chemical Engineering
Duration: 1980-1982
Date of issue: April 23, 1982
Place of issue: Budapest, Hungary
Number of diploma: 7019
I received the diploma with high achievement award.

Scholarship
University of Tromso, Norway:
Activity: synthesis of new type of heterocyclic compounds
Duration: 6 month
Date: 1984

Ph.D. degree in pharmaceutical chemistry:
Technical University of Budapest
School of Chemical Engineering
Date of issue: November 11, 1985
Place of issue: Budapest, Hungary
Number of issue: 4010
I received the Ph.D. degree with qualification "summa cum laude" .

Candidate of Sciences (CSc) degree in pharmaceutical chemical science
Hungarian Academy of Sciences
Date of issue: April 11, 1990
Place of issue: Budapest, Hungary
Number of issue: 13153

Title of Europa engineer, Eur. Ing.
FEANI, European Association of National Societies of Engineers
Date of issue: March 28, 1997
Place of issue: Paris, France
Number of issue: 22204 HU

Fields of activity and positions:

1977-1981 EGIS Pharmaceuticals, Chemical Production I., Budapest, Hungary
position: production leader
activity: direction and development of manufacturing of bulk pharmaceuticals

1981-1983 EGIS Pharmaceuticals, Pilot Plant., Budapest, Hungary
position: engineer for development
activity: development of novel drug products, new processes, improved processes, upscalings, plant start ups

1983-1984 EGIS Pharmaceuticals, Synthetic Department II., Budapest, Hungary
position: research engineer
activity: synthesis of biologically active compounds

1984-1990 EGIS Pharmaceuticals, Synthetic Department II., Budapest, Hungary
position: research associate
activity: synthesis and design of novel ring systems with biological activity

1990-1993 Cancer Research Institute, Tempe, Arizona, USA
position: research associate
activity:synthesis of new derivatives of D-10; separation and structure elucidation of natural compounds

1993-1994 EGIS Pharmaceuticals, Synthetic Department II., Budapest, Hungary
position: senior research associate
activity: synthesis and design of novel ring systems with biological activity

1994-2000 EGIS Pharmaceuticals, Synthetic Department I., Budapest, Hungary
position: head of department
activity: direction of original and generic projects

2000- EGIS Pharmaceuticals, Chemical Research Division., Budapest, Hungary
position: deputy head of division
activity: management of original chemical research at EGIS

Experience abroad:
(lectures, conferences)

USA, England, Scotland, France, Norway, Switzerland, Netherlands, Bulgaria, Slovakia, Spain

Publications:

patents: 51
printed papers: 20
lectures: 49

Membership of national and international organizations:

Association of Hungarian Chemists
Committee of the Hungarian Academy of Sciences for Heterocyclic Chemistry
Committee of the Hungarian Academy of Sciences for Pharmaceutical Chemistry

Budapest, March 16., 2003

Dr. József Barkóczy